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THE EFFECT OF IMMOBILIZATION AND 3(β -AMINOETHYL)-1,2,4-TRIAZOL ON THE CALCIUM CONTENT IN GASTRIC TISSUES OF GUINEA PIGS DURING THE FORMATION OF EXPERIMENTAL ULCERS

L.L. Grechishkin and K. Ritling

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16. Abstract The Ca^{2+} ions content in the blood plasma and gastric tissues of guinea pigs during experimental ulceration provoked by a 12-hour immobilization or through introduction of 3(β -aminoethyl)-1,2,4-triazol--a histamine analog--was measured by using atom absorption spectrophotometry. A sharp fall (to 79% (317 γ/g)) in the concentration of calcium in gastric tissues upon immobilization and after administration of the histamine analog--down to 71% (287 γ/g)--was recorded, while the calcium level in controls stood at 398 γ/g . Similar shifts were seen to occur in the blood plasma as well. According to the authors this implies that under the effect of different action tissue dystrophy develops by following a common mechanism involving not only the adenyl cyclase system, but that of calcium ion metabolism as well.					
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THE EFFECT OF IMMOBILIZATION AND 3(β -AMINOETHYL)-1,2,4-TRIAZOL ON THE CALCIUM CONTENT IN GASTRIC TISSUES OF GUINEA PIGS DURING THE FORMATION OF EXPERIMENTAL ULCERS

L.L. Grechishkin and K. Ritling

Department of Pharmacology, USSR Academy of Medical Sciences, Institute for Experimental Medicine, Leningrad, Rostok University Institute of Pharmacology (GDR)

In works of researchers from the school of S.V. Anichkov, it has been shown that a considerable liberation of tissue catecholamines and consequent depletion of their reserves and decrease in energy metabolism occurs when neurogenic dystrophy of the gastric mucous membrane of rats develops (S.V. Anichkov et al., 1967). /87*

It is known that the action of many hormones and biogenic monoamines, among them catecholamines, is transformed through the action of the cellular adenyl cyclase system and causes increased production of cyclic 3',5'-aminophosphate (3',5'-AMP), which is an intracellular mediator of various biochemical processes (Robinson et al., 1971; Liddle and Hardman, 1971). The energy of this compound may be realized only in the presence of free Ca^{2+} ions, and so a change in their tissue concentrations has a material effect on the level of cell metabolism and function (Rasmussen, 1970).

We studied calcium content in the gastric tissue and blood plasma of guinea pigs during the formation of experimental gastric ulcers. Center-reflexive (immobilization) and peripheral (histamine receptors) methods of pathological action were used here.

Methods of Study

In order to produce experimental gastric ulcers, guinea pigs weighing 250-300 g. were kept without food for 12 hours and then divided into groups (2 experimental and control). Immobilization of the animals of the first group was accomplished using metal screens for

*Numbers in the margin indicate pagination in the foreign text.

18 hours at an ambient temperature of 15-17°. Guinea pigs of the second group were injected intraperitoneally with a triazole analog of histamine--3(β -aminoethyl)-1,2,4-triazol--in a dose of 1 mg/kg, given twice with an interval of 6 hours (Lin and Harris, 1970). The control animals (3rd group) were injected with an inert salt solution and they were kept in cages without being fed. In all, 85 animals were used in the experiments.

All of the animals were decapitated 18 hours after the beginning of the experiment. The volume and acidity of the gastric contents were determined, the number of ulcers and erosions in the mucous membrane was counted, arterial blood samples were taken from the carotid artery (1 ml), and tissue samples were taken from the gastric wall of the lesser curvature in the pyloric area.

In order to determine Ca^{2+} content, the tissue samples (80-120 mg) were dessicated at 80° until reaching a constant weight, then burned in a quartz crucible at a retort furnace temperature of 800°. Ash residue was dissolved in 1 ml 1 N nitric acid, after which the solution was brought to a volume of 5 ml with demineralized water. The blood was centrifugated at 2000 RPM for 15 minutes and 4.5 ml demineralized water was added to 0.5 ml plasma. All samples were kept frozen until they were studied.

Content of Ca^{2+} in the samples was determined using an atomic absorption spectrometer produced by Instrumentation Lab. Inc., adjusted to a resonant line of 4227 angstroms. All the data were statistically worked up and analyzed using certainty criteria.

Results

Numerous gastric mucous membrane defects (ulcers and hemorrhagic erosions located in both the glandular and pregastric areas) were noted in all animals of the experimental groups, without exception, following the indicated pathologic influences. The number of these lesions in one average animal which had been subjected to immobilization amounted to 2.4, and in the group of animals subjected to the influence of the

histamine analog--3.6. There were no ulcers in the overwhelming majority of guinea pigs in the control group, and solitary erosions were detected only in 3, which, as we know, is sometimes found in these animals following prolonged hunger; the average number of lesions in control animals was 0.1.

The stomachs of guinea pigs which received the histamine analog were filled with gastric fluid (17.0 ± 6.2 ml) having an acute acidic reaction (pH 2.6); in animals which were subjected to immobilization, on the other hand, there was a moderate quantity of mucous fluid in the stomach contents (3.6 ± 1.1 ml) having a low acidity (pH 4.5).

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Ca^{2+} content in the gastric tissue of all experimental animals sharply and reliably decreased. In the guinea pigs of the control groups, calcium content averages 398 ± 12 μg per 1 g raw tissue, in those subjected to immobilization-- 317 ± 14 $\mu\text{g/g}$, and in those which received the histamine analog-- 287 ± 11 $\mu\text{g/g}$, i.e., 79 and 71% of the control level, respectively (see Table).

CALCIUM CONTENT IN BLOOD PLASMA AND GASTRIC TISSUES OF GUINEA PIGS DURING THE FORMATION OF EXPERIMENTAL ULCERS

	Control	Immobilization (12 hr at 16°)	P	Injection of 3(β -amino-ethyl)-1,2,4-triazol (1mg/kg)	P
Average number of ulcers in the stomach of 1 animal	0.1	2.4		3.6	
Concentration of Ca^{2+} :					
Gastric tissue (in mcg/g)	398 ± 12	317 ± 14	<0.05	287 ± 11	<0.05
Blood plasma (in mcg/ml)	81.7 ± 1.6	53.4 ± 1.7	<0.05	75.0 ± 1.6	<0.05
Gastric fluid:					
Volume (in ml)	17.0 ± 6.2	3.6 ± 1.1	<0.05	17.0 ± 6.2	<0.05
pH	2.6	4.5		2.6	

Calcium content in the blood plasma of the experimental animals also was decreased, and most significantly in those animals which had been subjected to immobilization: calcium content in them was equal to 53.4 ± 1.7 $\mu\text{g/ml}$, i.e., 65% of the control level (81.7 ± 1.6 $\mu\text{g/ml}$).

In the animals which received the histamine analog, the decrease in blood calcium concentration was considerably lower (75.0 ± 1.6 $\mu\text{g/ml}$, or 91%).

Discussion of Results and Conclusions

Gastric mucous membrane secretory cell function depends not only on the constant formation of cyclic 3',5'-AMP, but also on their optimally high concentration of calcium ions (Bersimbaev et al., 1971; Bieck et al., 1973; Lavine and Wilson, 1971; Kasbekar, 1972). In our experiments, the sharp decrease in gastric tissue calcium content during the period of ulcer formation was observed following both general neurogenic action and injection of the histamine analog. This qualitative identity of results for differing types of action may apparently be explained by the fact that both pathologic mechanisms have a common final point of application in the cell, and involve the adenylyl cyclase system, activation of which occurs in the first case through endogenous catecholamines liberated under the influence of mobilization (S.V. Anichkov et al., 1969), and in the second--through a histamine analog (Ruoff and Sewing, 1973).

Reverse Ca^{2+} transport from the surrounding cytoplasm is sharply increased during extreme and prolonged activation of membranous adenylyl cyclase, which probably also leads to a decrease in the concentration of these ions within the cell itself and, as a result of this, to a decrease in its energy potential, disruption of metabolism, and, in the final phase, to tissue destruction with the formation of ulcers.

The peptic factor in development of these lesions, apparently, does not play a commanding role, since experimental ulcers also formed in the stomach cavity of experimental animals where "aggressive" gastric fluid was lacking. Gastric contents in these animals consisted of mucous fluid with a pH 4.5 and a volume of 3.6 ± 1.1 ml; the stomachs of animals which had been subjected to the effects of the histamine analog were filled with a highly acidic fluid (pH 2.6).

The blood plasma calcium level in all experimental guinea pigs

was also lowered. However, this decrease was more pronounced in immobilized animals (65%) than in the animals which had the histamine analog (91%). These variations may be explained by the fact that immobilization is a general neurogenic influence which alters many body regulator systems, among them hormonal, which leads to disruption of overall homeostatis. In contradistinction to this, the action of the histamine analog is aimed only at specific receptors and has a peripheral character.

Our studies indicated that pathologic influences of differing types cause qualitatively identical alterations in gastric tissues-- a sharp decrease in calcium ion concentration and formation of ulcers. This permits us to propose that the dystrophic process at the cell level is caused by a common mechanism, in which both the adenyl cyclase system and calcium ion exchange are involved.

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